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EXAMINER	
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ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,587	ZOU ET AL.	
	Examiner	Art Unit	
	KARLHEINZ R. SKOWRONEK	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-13,15-27 and 30* is/are pending in the application.

4a) Of the above claim(s) *15-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-13, and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-6, 8-13, 15-27, and 30 are pending.

Claims 7, 14, and 28-29 are cancelled.

Claims 15-27 are withdrawn as being directed to a non-elected invention.

Claims 1-6, 8-13, and 30 have been examined.

Claims 1-6, 8-13, and 30 are rejected.

Priority

This application is the national phase application of PCT/US03/01636 filed on 17 January 2003 and claims the benefit of Provisional Application No. 60/349874 filed on 18 January 2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 25 November 2008 was filed after the mailing date of the First Action on the Merits on 07 December 2006 but before prosecution was closed. The submission is in compliance with the provisions of 37 CFR 1.97(c). Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 101

Response to Arguments

Applicant's arguments, see remarks p. 7-8, filed 20 November 2008, with respect to the rejection of claims 1-6, 8-13, and 29-30 as non-statutory under 35 USC 101 have been fully considered and are persuasive. The rejection of claims 1-6, 8-13, and 29-30 has been withdrawn in view of the amendment of claims 1 and 8 to recite a physical transformation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection is necessitated by amendment of the claims

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must perform multiple hybridizations of genomic DNA to microarrays to calculate corrected hybridization signals and use the signals to calculate an expression level for a gene. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The description describes determining gene expression levels from RNA samples (p.33). The specification also describes perform genomic hybridizations to identify gene probes that bind to the genomic DNA from probes that do not bind (p.23). The description does not provide detailed guidance to calculating gene expression from genomic DNA hybridization array data.

c) The description provides working examples of calculating gene expression from RNA or cDNA hybridized to arrays. The description does not provide working examples of calculating gene expression only from genomic DNA hybridized to arrays.

d) The nature of the invention, gene expression quantification, is complex.

e) The prior art does not show calculating gene expression only from genomic DNA hybridized to arrays. Kincaid et al. (Information Visualization, Vol. 4, p. 176-190, 2005) shows that genomic hybridizations to arrays measures anomalies in DNA copy number. Kincaid et al. shows genomic hybridization arrays are designed to measure the abundance of genomic DNA targets, in contrast to mRNA targets of gene expression arrays

f) The skill of those in the art of gene expression is high.

g) The predictability of calculating gene expression only from genomic DNA

hybridized to arrays is unknown in the prior art.

h) The claims are broad in that they only require genomic DNA for the determination of gene expression.

The skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence that genomic DNA alone can provide for the determination of gene expression. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss the determination of gene expression levels from genomic hybridizations alone. Finally, said practitioner would turn to trial and error experimentation to determine a relationship between gene expression and genomic hybridization array data. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Pietu et al. (Genome Research, Vol. 6, p. 492-503, 1996).

The claims are directed to a method of correcting oligo probe hybridization signals in which signals of multiple hybridizations are measured, a correction coefficient is calculated for each probe such that the probe's average is equal to a constant,

correcting each probe signal with the correction coefficient and outputting the corrected signal.

Pietu et al. shows the analysis of hybridization signals from microarrays. Pietu et al. shows that signal intensities of multiple hybridizations are measured (p. 493, col. 2). Pietu et al. shows that each probe is divided by the average of all probes (p. 502, col.1). The correction of the signal intensity data in Pietu et al. reads on the limitations because Pietu et al. show each probe's intensity is corrected by a coefficient that is 1/(average intensity), therefore if the average intensity is multiplied by the same coefficient the result is a constant, that is 1. This teaching reads on the limitation that each probe's signal is corrected using a coefficient such that the probe's average is equal to a constant. Pietu et al. show the probes' signal intensities are corrected and output (p. 502, col. 1). Pietu et al. shows the calculation of standard deviation and average (p.502, col. 2). Pietu et al. shows the determination of an uncertainty coefficient that is a ratio of the average to the standard deviation (p.502, col. 1).

Response to Arguments

Applicant's arguments filed 20 November 2008 have been fully considered but they are not persuasive. Applicant argues that Pietu et al. fails to teach all the elements of the claim 1, specifically genomic DNA hybridizations and a microarray. The argument is not persuasive. With respect to the element of genomic DNA hybridizations, Pietu et al. shows that hybridizations were performed with genomic DNA (p. 495, col. 2). With respect to applicant's argument that Pietu et al. does not show a microarray, the term microarray is given the broadest reasonable interpretation. The specification does not

provide a definition for "microarray" that would require a narrower interpretation for the term microarray. The arrays of Pietu et al. are microarrays (figure 1). The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jelinsky et al. (Mol. Cell. Biol., Vol. 20, No. 21, p.8157-8167, November 2000), in view of Wohlgemuth et al. (US PGPUB 2007/0037144).

The claims are directed to a method of correcting probe hybridization signals by measuring signals from each oligo probe in multiple hybridizations; calculating a correction coefficient for the probes such that the signal average is equal to a constant; and correcting the signal for the probes using the calculated correction coefficient. In some embodiments, an average and standard deviation for the signals observed for each probe are calculated. In some embodiments, an uncertainty coefficient, called signal to noise ratio, is calculated based on the ratio of the average to standard deviation.

Jelinsky et al. teach a method of correcting oligo probe hybridization signals (p. 8157, col. 2, para 2, line 1-22). Jelinsky et al. show that 4 arrays of 6218 probes each were incubated with 10ug RNA, washed and scanned (p. 8157, col. 2, para 2, line 2-6). Jelinsky et al. show that a correction coefficient is calculated for the arrays such that the average of the intensities on the array is equal to a constant, 300 (p. 8157, col. 2, line16-18). Jelinsky et al. teach that the scaling allows the arrays to be directly compared with each other (p. 8157, col. 2, line18-19).

Jelinsky et al. do not show the calculation of individual correction coefficients for individual probes where the average signal of the individual probes is made to equal a constant.

Wohlgemuth et al. show a method of measuring DNA hybridization. Wohlgemuth et al. teach individual probes or median background subtracted signals (BGSS) can be scaled to be between 0 and 1 [0212]. Wohlgemuth et al. teach that scaling is desirable because it has the advantage of facilitating the comparison of data between different experiments [0212]. Wohlgemuth et al. teach that DNA is genomic DNA [0091]. Wohlgemuth et al. show that an average and standard deviation for the signals observed for each probe are calculated [207]. Wohlgemuth et al. show that an uncertainty coefficient, called signal to noise ratio, is calculated based on the ratio of the average to standard deviation [0207]. Wohlgemuth et al. show that probes that do not have a certain predetermined signal to noise ratio are disregarded. In Wohlgemuth et al., the signal to noise ratio is calculated as mean divided by the standard deviation. The signal to noise ratio is the inverse of the coefficient of variation, standard deviation divided by the mean. Wohlgemuth et al. teach that if the signal to noise ratio is less than 3 which is equivalent to having a coefficient of variation that is greater than 0.33 the data is flagged but used, reading on a predetermined value that is approximately 1.0 [0728]. As the signal to noise ratio decreases, it approaches 1. When the signal to noise ratio is equal to 1, the ratio indicates that signal cannot be distinguished from the noise, indicative of data of poor quality. Similarly, for the inverse of the signal to noise ratio, coefficient of variation (CV), as the CV increases to approach 1, the quality of the data

becomes poorer and less reliable. Wohlgemuth et al. teach that if a replicate feature is of poor quality it can be disregarded and the remaining features used to represent the gene [0200].

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of correcting oligo probe hybridization signals of Jelinsky et al. with the individual probe scale factors of Wohlgemuth et al. because Wohlgemuth et al. shows that scaling provides the advantage of facilitating the comparison of data between different experiments. As the signal to noise ratio decreases, it approaches 1. When the signal to noise ratio is equal to 1, the ratio indicates that signal cannot be distinguished from the noise, indicative of data of poor quality. Similarly, for the inverse of the signal to noise ratio, coefficient of variation (CV), as the CV increases to approach 1, the quality of the data becomes poorer and less reliable.

Response to Arguments

Applicant's arguments filed 20 November 2008 have been fully considered but they are not persuasive. Applicant argues that Wohlgemuth et al. fails to show a correction factor as set forth in claim 1. The argument is not persuasive. The correction factor recited requires the average to equal one. This is interpreted to describe the equation $correctionFactor \cdot average = 1$ or. Thus using the correction factor to correct or scale signal is then interpreted to describe the equation

$correctedSignal = correctionFactor \cdot signal$ alternatively, $correctedSignal = \frac{signal}{average}$.

Wohlenguth et al. shows that the BGSS or background corrected signal for each probe is "corrected" with a factor that is 1 divided by the average; in other words,

$corrrectionFactor = \frac{1}{average}$. Wohlgemuth et al. shows in [0212], line 5-6, BGSS are scaled to a factor such as a mean or average. Wohlgemuth shows in [0214], line 1-6, that individual expression levels may be corrected between different experiments allowing direct comparisons. Wohlgemuth et al. shows that a scaling factor maybe used to adjust or correct individual expression levels as in equation (0.3), $S_i = \frac{BGSS_i}{a}$ where S_i is the corrected feature signal and $BGSS_i$ is the feature signal and a is the average signal. Although, Wohlgemuth shows that (a) in equation (0.3) can be the average of all probes in the array, Wohlgemuth et al. suggests other averages could be used as in [0212], line 5-6. Thus, one of ordinary skill in the art at the time of invention could have corrected the signal for a particular feature on a particular array by dividing that feature's signal by the average signal for that feature represented on multiple arrays to generate a corrected signal, because Wohlgemuth et al. suggests individual expression levels may be corrected between different experiments allowing direct comparisons. The rejection is maintained.

The following rejection is reiterated from the previous action.

Claim 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jelinsky et al. (Mol. Cell. Biol., Vol. 20, No. 21, p.8157-8167, November 2000), in view of Wohlgemuth et al. (US PGPUB 2007/0037144) as applied to claims 1-5 above, and further in view of Pinkel et al. (US Pat 5,830,645).

The claims are drawn to determining a dynamic range for DNA binding.

Jelinsky et al. (Mol. Cell. Biol., Vol. 20, No. 21, p.8157-8167, November 2000), in view of Wohlgemuth et al. (US PGPUB 2007/0037144) as applied to claims 1-5 above do not teach determining a dynamic range for DNA binding.

Pinkel et al. show a method of comparative genomic hybridization. Pinkel et al. show that the method provides increased sensitivity, more precise localization of chromosomal abnormalities and which can detect differences in levels of gene expression are particularly desirable for the diagnosis of disease (col. 2, line 23-26). Pinkel et al. show that serial dilutions of pairs of fluorochrome in known relative proportions can also be analyzed to determine the accuracy with which fluorescence ratio measurements reflect actual fluorochrome ratios over the dynamic range permitted by the detectors and membrane fluorescence (col. 8, line 44-49).

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of correcting oligo probe hybridization signals of Jelinsky et al., in view of Wohlgemuth et al. as applied to claims 1-5 above and in further view of the method comparative genomic hybridization by Pinkel et al. because Pinkel et al. show that the method provides increased sensitivity, more precise localization of chromosomal abnormalities and which can detect differences in levels of gene expression are particularly desirable for the diagnosis of disease.

Response to Arguments

Applicant's arguments filed 20 November 2008 have been fully considered but they are not persuasive. Applicant argues that Pinkel et al. does not cure the

difficiencies of Jeninsky et al. in view of Wohlgemuth et al. The argument is not persuasive for the reasons given above. The rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571)272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. R. S./
Examiner, Art Unit 1631

3 February 2009

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631